

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Giles et al.



Group Art Unit: N/A

Serial Number 10/603,824

Examiner: N/A

Filed June 26, 2003

Atty Docket: DEH058

For: Mass Spectrometer

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The below identified communication(s) or document(s) is(are) submitted in the above application or proceeding:

☒ Priority Document(s) 3

GB 0214898.9

GB 0303055.8

GB 0308419.1

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Respectfully submitted,

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Date: August 8, 2003



INVESTOR IN PEOPLE

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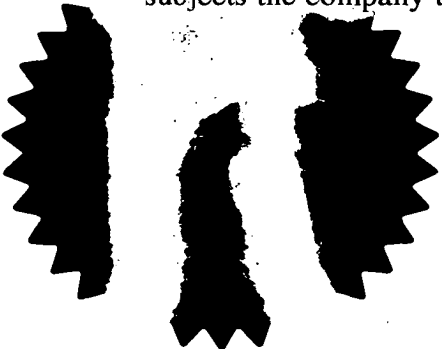
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I also certify that by virtue of an assignment registered under the Patents Act 1977, the application is now proceeding in the name as substituted.

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Signed

Dated 15 July 2003



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GB0214898.9

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:-

MICROMASS UK LIMITED
Incorporated in the United Kingdom
Atlas Park
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ADP No. 07649676002

Patent 1977
(Rule 107)

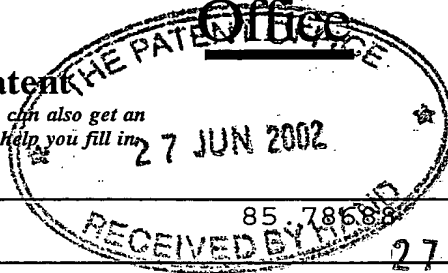
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Request for grant of a patent

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0214898.9

1. Your reference

2. Patent application number
(The Patent Office will fill in this part)

28JUN02 E729253-1 D00027
P01/7700 0.00-0214898.9

3. Full name, address and postcode of the
or of each applicant (underline all surnames)

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SECTION 30 (1977 ACT) APPLICATION FILED 02.06.03

Patents ADP number (if you know it) 06996102001

If the applicant is a corporate body, give
country/state of incorporation UK

4. Title of the invention

Mass Spectrometer

5. Name of your agent (if you have one)

Frank B. Dehn & Co.

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number (if you know it) 166001

6. If you are declaring priority from one or more
earlier patent applications, give the country
and the date of filing of the or of each of these
earlier applications and (if you know it) the or
each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right
to grant of a patent required in support of
this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
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Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
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11. I/We request the grant of a patent on the basis of this application.

Signature

Date 26 June 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

P.M. Jeffrey
01273 244200

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Travelling Wave Ion Guide as a Mobility Analyser

Introduction to RF ion Guides

Radio Frequency (RF) ion guides are commonly used for confining and transporting ions. All such ion guides use an arrangement of electrodes with an RF voltage applied between neighbouring electrodes such as to produce a pseudo-potential well or valley. This pseudo-potential well can be arranged to confine ions, and may be used to transport ions by acting as an ion guide. Its use as an ion guide is well known, and can be very efficient.

The RF ion guide can still function efficiently as an ion guide even at quite high pressures, where ions are likely to undergo frequent collisions with residual gas molecules. The collisions with gas molecules may cause the ion to scatter and lose energy, but the pseudo potential well generated by the RF ion guide still acts to confine the ions. In this respect the RF ion guide has an advantage over the "guide wire" type of ion guide, in which a DC voltage is applied to a central wire running down the centre of a conducting tube. In this arrangement ions are held in orbit around the central guide wire. However, in the "guide wire" type of ion guide, if ions undergo many collisions with gas molecules they will lose energy and will eventually collapse into the central guide wire and be lost.

As a consequence of their ability to transport ions at relatively high pressures, RF ion guides are the preferred type of ion guide for a number of applications in mass spectrometry apparatus. In particular they are used in "gas collision cells" in which relatively low energy ions (i.e. ions with energies between 10 and 1000 eV) undergo multiple collisions with gas molecules to induce ion fragmentation or decomposition. Similarly, they are used in "gas reaction cells" in which low energy ions (i.e. ions with energies between 0.1 eV and 10 eV) undergo collisions with gas molecules to form adjunct ions.

RF ion guides are also used to transport ions through chambers at intermediate pressures (0.001 ~ 10 mbar), for example from an ion source in a chamber at high pressure (e.g. an atmospheric pressure ion source) to a mass analyser in a chamber at very low pressure. Such mass analysers include the quadrupole ion trap, the quadrupole mass filter, the time-of-flight mass spectrometer, the magnetic sector mass spectrometer, and the Fourier Transform Ion Cyclotron Resonance mass spectrometer (FTICR). In both instances ions can be efficiently transported despite undergoing many collisions with gas molecules causing the ions to be scattered and to lose energy.

It is well known that ion transit times through RF only ion guides, collision cells and reaction cells, when operated at sufficiently high gas pressure, can be long due to reduction of axial ion energy by collisions with the gas. It is also known that the continued presence or absence of an incoming ion beam, and any surface charging leading to axial potential barriers, can further affect the transit time.

As has been already mentioned, when an ion collides with a gas molecule it may get scattered and lose kinetic energy. If the ion undergoes a large number of collisions,

perhaps more than 100 collisions, the ion will lose all its forward kinetic energy. The ions will now have a mean energy equal to that of the surrounding gas molecules. They will now appear to move randomly within the gas due to continuing random collisions with gas molecules. Hence, under some operating conditions, ions being transported through an RF ion guide at an intermediate gas pressure will lose all their forward motion. Under these conditions the ions will never emerge from the exit of the ion guide.

In practice ions may still continue to move forwards for other reasons. It is normally assumed that ions may continue to move forwards due to the bulk movement of gas (a gas dynamic "wind") blowing the ions through the ion guide, or due to space charge caused by continual ingress of ions into the device (electrostatic repulsion from ions arriving from behind) effectively pushing the ions through the ion guide (1). Without these influences it is known that under certain conditions ions can, in effect, come to a standstill in the ion guide and not emerge at the exit.

A known means for driving ions through an RF ion guide at intermediate pressures is the use of an axial electric field. To ensure the ions emerge, or simply to reduce their transit time, it has become current practice to apply an axial voltage gradient along the ion guide. The axial electric field may be applied in a number of ways. For example, axial electric fields may be applied to ion guides using multipole rod sets by the use of segmented rods with a DC voltage between successive rods (2), by the use of inclined or tapered rods (3), or by the use of resistive rods with a DC voltage gradient along their length (3). Axial fields may be applied to ion guides using stacked ring sets by applying a DC voltage to successive rings (4) or groups of rings (5). Axial fields may also be applied by the use of additional electrodes, usually in the form of cylinders, external to the ion guide such that some of this axial field penetrates into the ion guide itself (3). In all these cases the axial electric field causes the ions to accelerate forwards after each collision with a gas molecule. A very weak field, in the region of 0.1 to 1 volt/cm, is adequate for pressures between 0.001 and 0.01 millibar. At higher pressures higher field strengths can be used.

In the pressure region above 0.001 millibar ions in an axial field will attain velocities according to their ion mobility. When such drift tubes are used in conjunction with a pulsed ion source then separation of species according to their ion mobility is achieved. The output of such a mobility spectrometer may be coupled to mass spectrometer to achieve charge state separation (6) to improve signal to noise.

Swept Mobility Extraction Guide

The new invention is a variation on the Travelling Wave Ion Guide (TWIG) (7) which entails superimposing a repeating pattern of electrical potentials along the length of the ion guide such as to form a periodic waveform, and causing the waveform to travel along the ion guide in the direction in which it is required to move the ions, and at the velocity at which it is required to move the ions.

The travelling wave device requires that an RF ion guide, such as a multipole rod set or stacked ring set, is segmented in the axial direction such that independent transient DC potentials can be applied to each segment, superimposed on top of the RF confining voltage and any constant DC offset voltage, whereby the DC potentials are changed temporally to generate a travelling wave in the axial direction.

At any instant in time a voltage gradient would be generated between segments to push or pull the ions in a certain direction. As the ions move in the required direction so would the voltage gradient. The individual DC voltages on each of the segments would be programmed to create a required waveform. Furthermore, the individual DC voltages on each of the segments would be programmed to change in synchronism such that the waveform would be maintained but shifted in the direction in which it is required to move the ions.

Consider now a stacked ring ion tunnel device (at a pressure such that an ion traversing its length undergoes many collisions) filled with ions such as may be generated by an electrospray or MALDI ion source. If the end plates of the tunnel have a slight positive voltage with respect to all the central plates then ions will be trapped in the device unable to surmount the potential barrier. After a certain time equilibrium will be reached where ions of all masses and mobilities are distributed along the length of the device [Figure 1]. If a voltage is then applied to the first electrode in the tunnel adjacent to one of the end plates the ions will be pushed down the device [Figure 2] by the local field variation according to the equation:

$$V_{\text{drift}} = K * E(x) \quad (\text{Equation 1})$$

where V_{drift} is the drift velocity of the ion K its mobility and $E(x)$ the electric field caused by the applied voltage. The electric field caused by the applied voltage rapidly decays to a negligible value just a few electrode spacings. The voltage is then rapidly switched to the next electrode and an ion that had enough time to drift at least one electrode spacing will experience the same force and move again. Those ions of low mobility may not have time to drift far enough to see the influence of the voltage when it switches to the next electrode and will be left behind. The voltage travels down the device from electrode to electrode "sweeping" those ions with a high enough mobility to follow it. The device acts as a high pass filter in that ions with mobilities above a chosen value can be ejected from the tunnel whilst the rest remain trapped in the device [Figures 3 & 4]. The sweep time of the device T_{sweep} may be then reduced to select a slightly lower mobility cut off ejecting those ions which have mobilities between the two cut off points. By gradually reducing the sweep time a complete mobility "scan" may be built up until the device is empty. Another way to scan the device is to increase the voltage progressively with each sweep collecting ions of ever decreasing mobility in the same way. Note that from equation (1) doubling the voltage will double the velocity of an ion. The resolution of the device is in part determined by the size of the sweep (T_{sweep}) time or Voltage increment. The smaller the step between adjacent sweeps the greater the resolution of the device.

The mode of operation described above builds up a mobility spectrum by a series of high pass experiments. Isolation of a particular range of mobilities i.e. bandpass operation may be achieved by employing a two stage device. Firstly ions with mobility $> X$ are passed through the device into a second empty stage [Figure 5]. The

travelling wave may be reversed sweeping ions back into the first stage [Figure 6]. This reverse sweep may be faster (or of a higher voltage) so that the required mobility range is left behind in the second stage [Figure 7].

The resolution of the travelling wave device has been modelled to include the effect of diffusion of ions. Diffusion effects degrade the resolution of conventional drift tube IMS devices there being a fundamental equation showing a relationship between the drift tube length and the applied axial voltage drop (8):-

$$\frac{|X|}{L} = \frac{0.173}{\sqrt{V}} \quad (\text{Equation 2})$$

where mod X is the spatial spread due to diffusion, L the drift tube length and V the applied axial voltage drop. To increase the resolving power of the mobility spectrometers longer drift tubes and higher voltages are traditionally employed. An advantage of the current invention is that only a relatively low voltage is required i.e. that which is applied to a single element, typically this would be 10 Volts or so at a pressure of ~ 2mBar. The SMEG device has been modelled as a series of elements with the voltage resident on each element for a certain time. Diffusion is introduced as a random scattering component over the time of residence of the voltage on an element. The program used to predict the behaviour of the device is shown in figure 8. The result shown in figure 9 predicts the complete separation of Gramicidin S and Leucine encephalin. This result is for a SMEG with 100 elements and a voltage of 7 volts on each plate. This result is comparable with the performance one would expect from a single pass drift tube of similar dimensions.

Further improvements in resolution may be achieved by sweeping the ions backwards and forwards through the same volume. This has the effect of increasing the effective length of the device without actually increasing its physical dimensions. Ions may be purged from the swept volume after the passage of the travelling wave by switching the RF off allowing ions to diffuse out of that portion of the device. After the desired number of passes of the same volume the ions may be allowed out of the device for further analysis.

Advantages over prior art

1) High Duty Cycle:

The new device can operate at 100% duty cycle as it is able to eject only those ions of desired mobility while storing the rest for further analysis. This is in contrast to a Field Asymmetric Ion Mobility Spectrometer (FAIMS) which is a scanning device whereby ions that are not transmitted are lost to the walls of the device.

2) Flexible timescale of ion ejection

The drift tube type works by admitting a short pulse of ions (known as the gate pulse) and allowing them to disperse in an electric field according to their mobility. By trapping ions prior to the drift tube they can be accumulated while the drift tube is dispersing ions and duty cycles approaching 100% may be achieved. The separation

is generally on the millisecond timescale so subsequent experiments must be amenable to this to be able to take advantage of the duty cycle. In the case of the charge state separation device the quadrupole must be scanned in synchronisation with the output of the drift tube. This can cause significant losses in ion transmission as ions that enter the quadrupole with a stable trajectory may find themselves unstable part way through the quad and so be lost. With the current invention the quadrupole can be set to a discrete mass to charge transmission window to match the desired mobility range ejected by the device. This means that the desired ions are stable in the quadrupole all through the device. The equivalent to a scanning experiment can be performed piecewise with no loss in duty cycle as unejected ions are still stored by the device.

3) No Gate pulse required:

To obtain high duty cycle with a drift tube type of mobility spectrometer when using continuous ion sources requires the use of a trapping stage. Ions are then admitted to the Drift tube using gate pulses which are narrow compared to drift times of ions. A spectrometer that disperses on the millisecond timescale therefore requires a gate pulse of the order of microseconds to achieve the best resolution. The use of such gate pulses result in mobility discrimination at the input to the device leading to lower sensitivity and skewed spectra. The SMEG device has no need for a narrow gate pulse as the device can be filled with a longer pulse and so avoids these problems.

4) Large voltages not required:

As can be seen from equation 1 a limiting factor comes from the spatial spread of the ions caused by diffusion. Drift tube devices employ large voltage drops across them to minimise this problem. The SMEG only requires a small voltage as the ions are localised at the active plate at any moment in time. Ten volts in a SMEG equates to ~ 1000 Volts on a drift tube with a 100 element device.

5) Folded multipass geometry:

As ions may be send backwards and forwards within the SMEG device greater resolution can be achieved in a more compact device than in a drift tube of similar dimensions. More passes of the device (in the second less populated region) lead to greater isolation of the desired species.

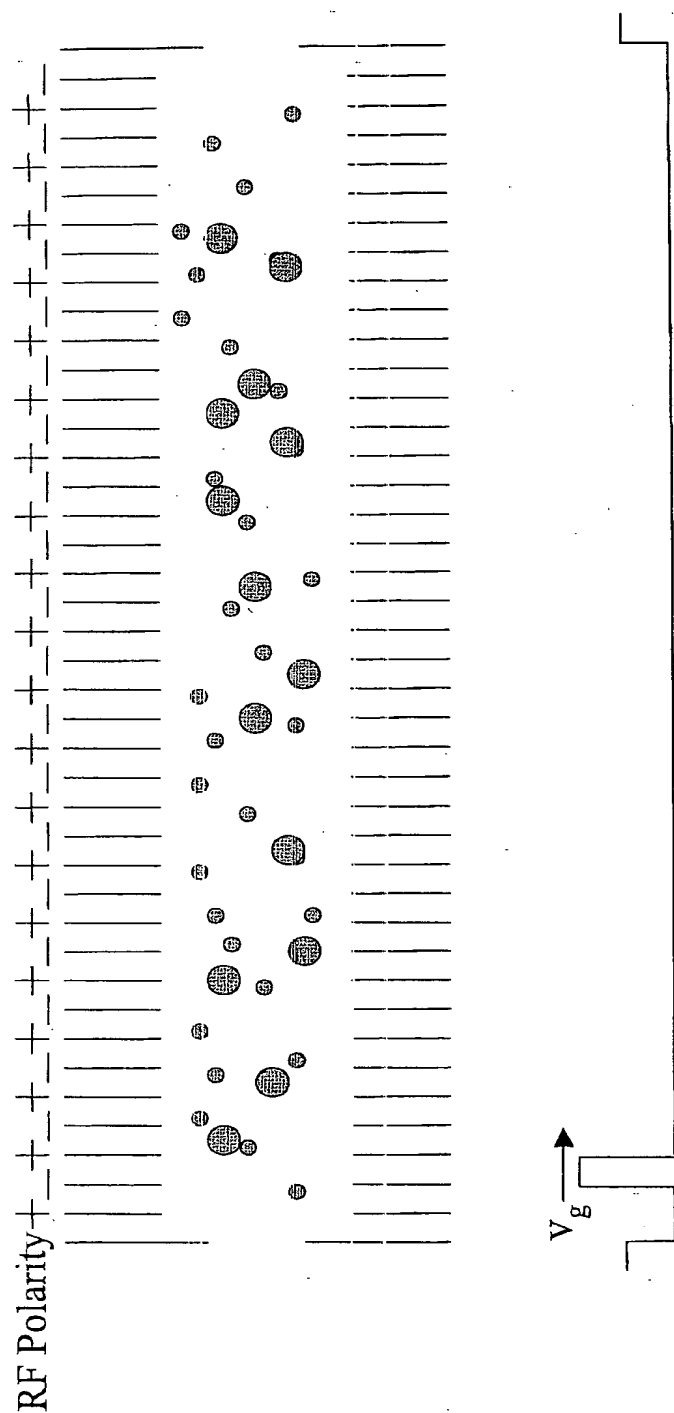


Figure 2. Travelling wave begins at one end of device

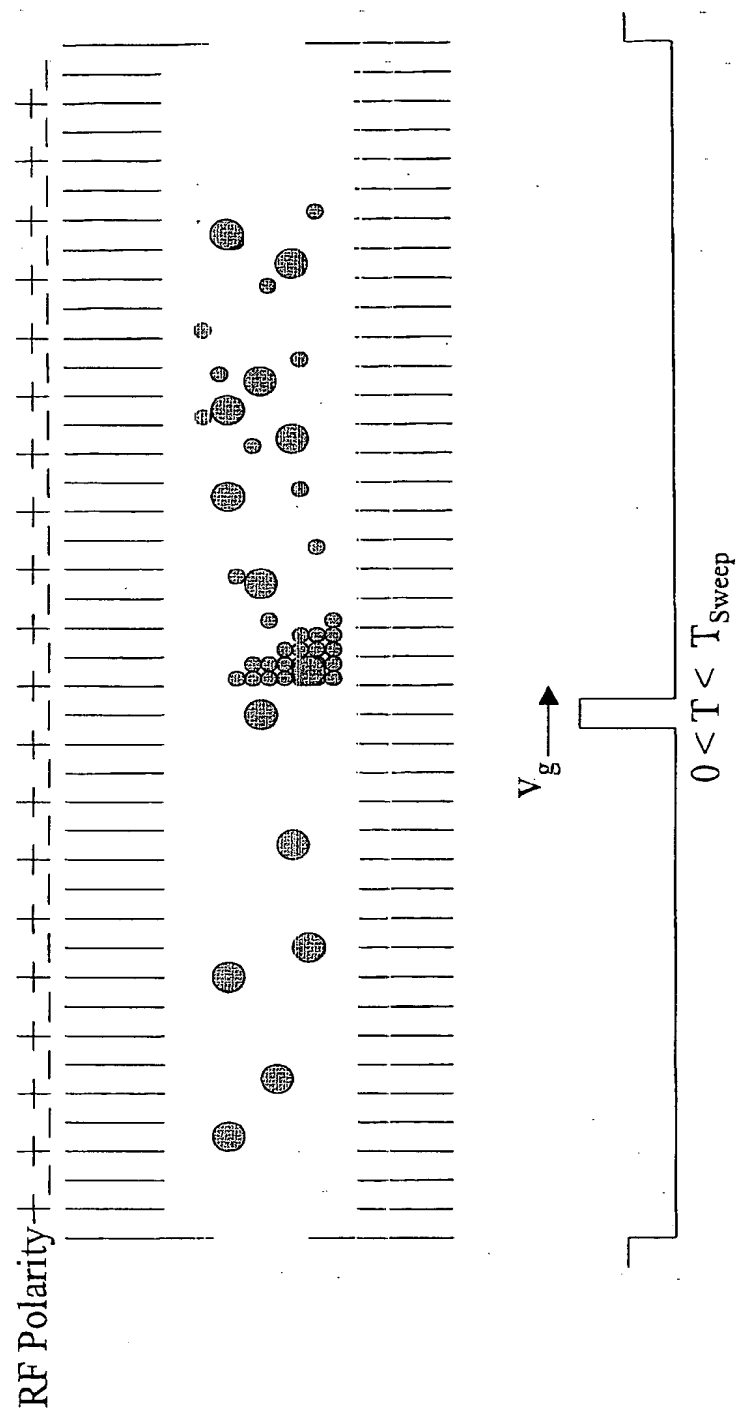


Figure 3. Travelling wave sweeping high mobility ions

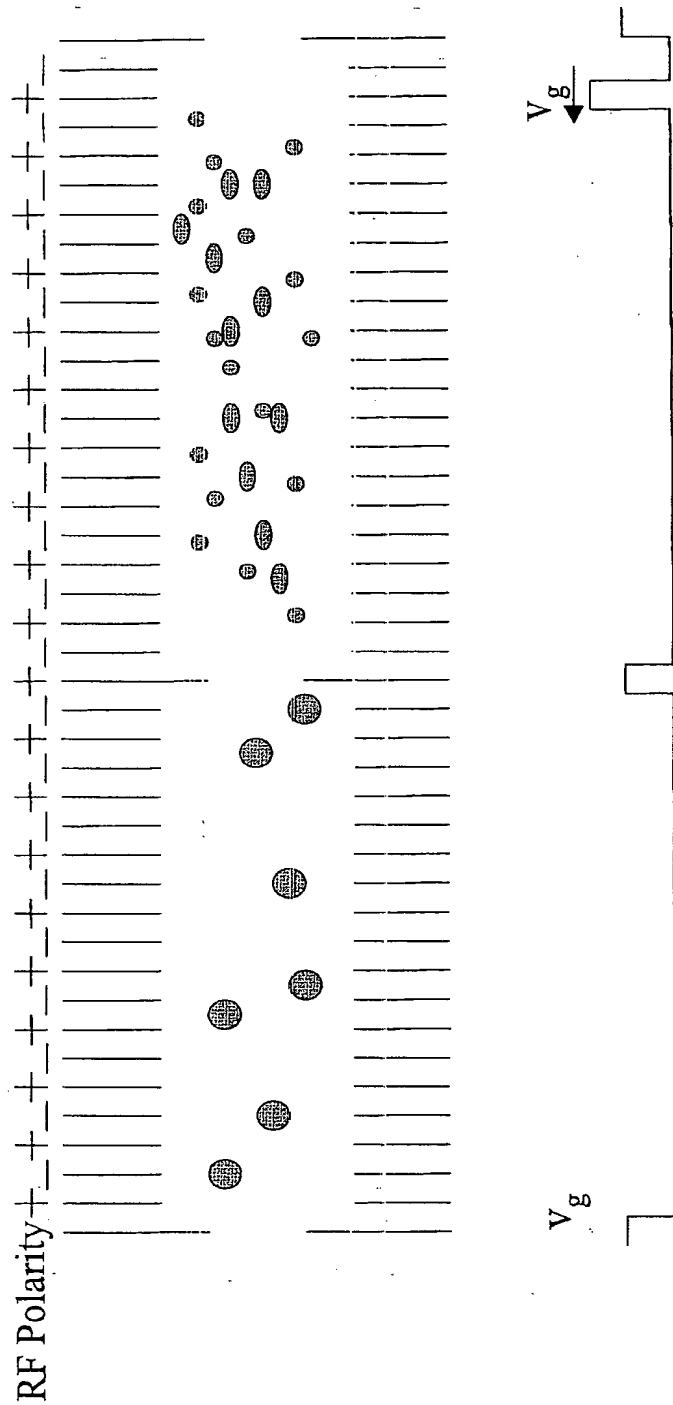


Figure 6. Higher mobility ions swept into second stage of device, wave direction reversed and intensity V_g reduced.

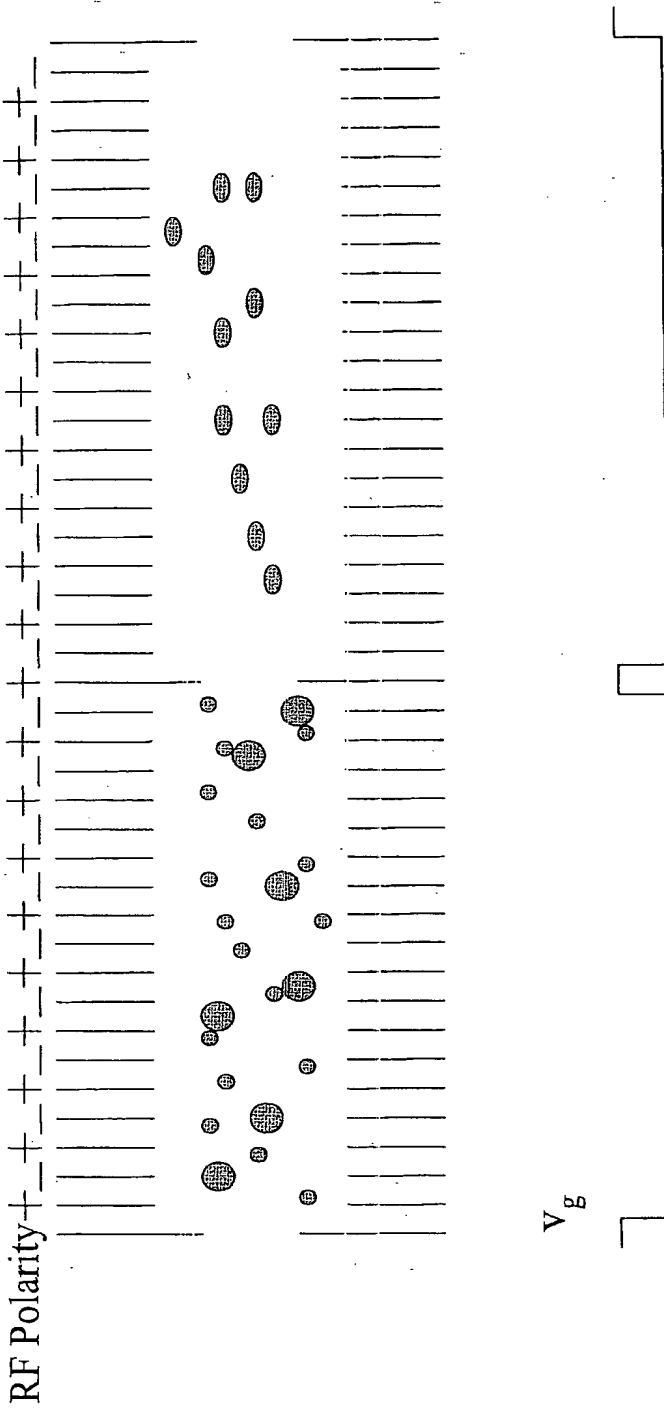


Figure 7. Intermediate mobility left behind in second stage (bandpass operation).

$$L := 1.5 \cdot 10^{-3} \quad V_p := 3.5 \quad T := 1.55 \cdot 10^{-5} \quad K := 6.6 \cdot 10^{-2} \quad N_{el} := 100 \quad N_{ion} := 1000$$

$$x_0 := 1.5L \quad c := K \cdot V_p \cdot 3.142 \frac{T}{4 \cdot L} \quad sig := \sqrt{2 \cdot K \cdot \frac{T}{42.465}} \quad a := \frac{3.142}{2 \cdot L} \quad SwT := N_{el} \cdot T$$

$$c = 1.875 \times 10^{-3} \quad a = 1.047 \times 10^3 \quad x_0 := 2.25 \times 10^{-3} \quad sig = 2.195 \times 10^{-4} \quad SwT = 1.55 \times 10^{-3}$$

$$f2(x_0) := \begin{cases} \text{for } i \in 1..N_{el} \\ \quad \text{deltadist} \leftarrow \text{rnorm}(1, 0, sig) \\ \quad x_0 \leftarrow \left[\frac{-\pi + \arcsin \left[\frac{(-\exp(2 \cdot c \cdot a) + \exp(2 \cdot c \cdot a) \cos(x_0 a) + 1 + \cos(x_0 a))}{(-\exp(2 \cdot c \cdot a) + \exp(2 \cdot c \cdot a) \cos(x_0 a) - 1 - \cos(x_0 a))} \right]}{a} \right] - L + \sum \text{deltadist} \text{ if } x_0 \geq 0 \\ \quad x_0 \text{ otherwise} \\ x_0 \end{cases}$$

$$f2(x_0) = -1.598 \times 10^{-4}$$

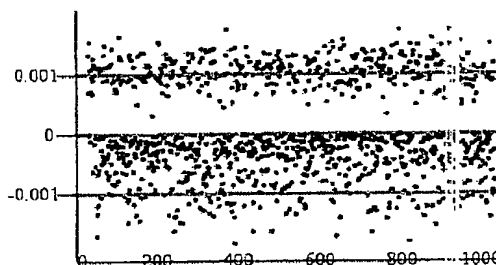
$$M := \begin{cases} \text{for } j \in 0..N_{ion} - 1 \\ \quad m_j \leftarrow f2(x_0) \\ m \end{cases}$$

$$M_0 = 1.33 \times 10^{-3} \quad M_{10} = -6.346 \times 10^{-4} \quad M_{20} = 1.113 \times 10^{-3} \quad M_{30} = 1.07 \times 10^{-3} \quad M_{40} = 1.12 \times 10^{-3}$$

Position relative to Nth element

$$f3(M) := \begin{cases} \text{cnt} \leftarrow 0 \\ \text{for } k \in 0..N_{ion} - 1 \\ \quad \text{cnt} \leftarrow \text{cnt} + 1 \text{ if } M_k \geq 0 \\ \text{OP} \leftarrow \frac{\text{cnt} \cdot 100}{N_{ion}} \\ \text{OP} \end{cases}$$

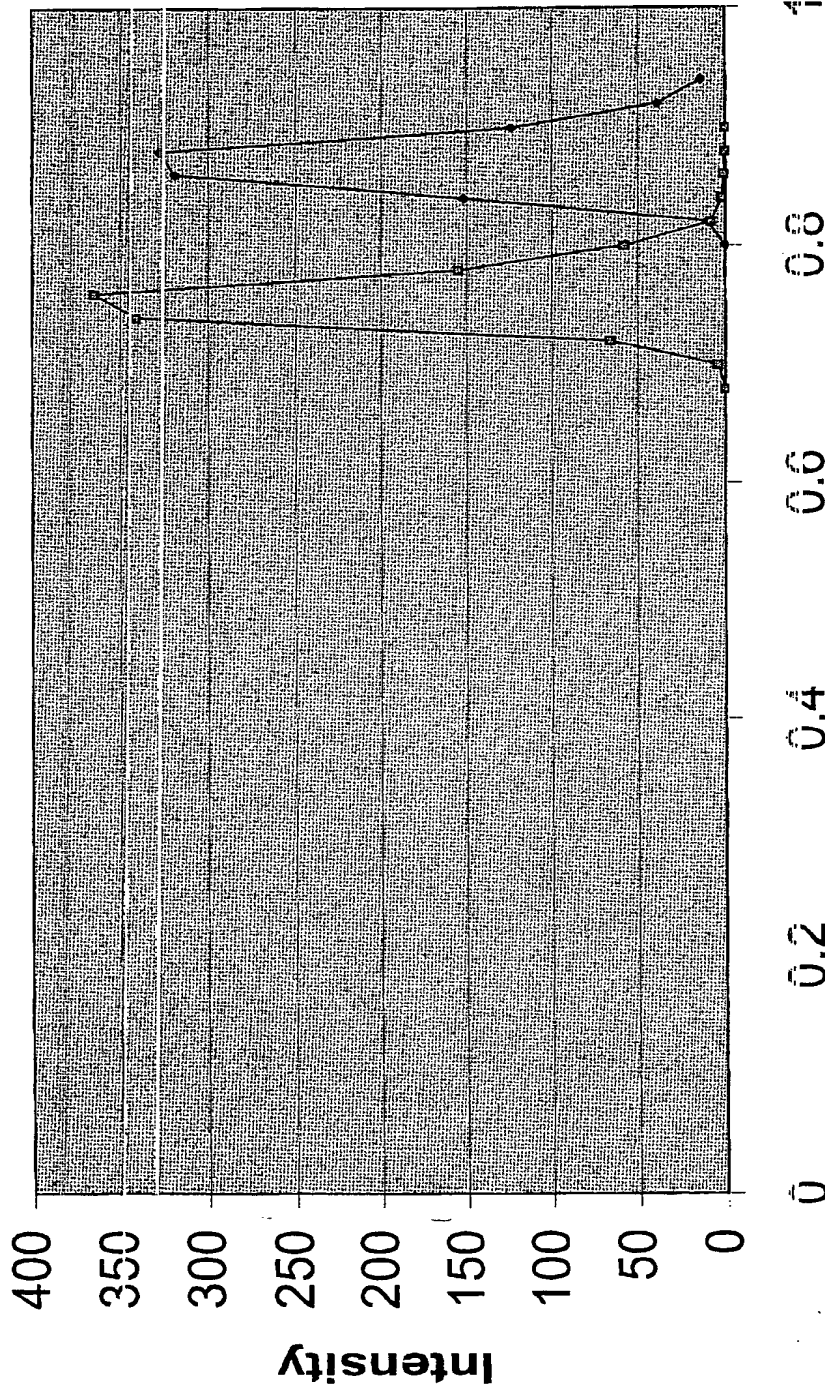
$$f3(M) = 35.2$$



M

Figure 8

LeuEnk V's Gram-s Mobilty (100 elememts, Vp = 7)



Sweep Time (mS)

Figure 9